**I. Remarks**

Claims 3-7, 9-16, 18, 19, and newly added claims 20-25 are pending in the subject application.

Claims 3-7 and 15-19 have been amended with this response. Support for the amendments to claims 3-6 is found throughout the instant specification and particularly in Examples 8 and 9. Support for the amendments to claim 7 is found throughout the instant specification and particularly at page 12, lines 1-8 and in Examples 8 and 9. Support for the amendments to claim 16 is found throughout the instant specification and particularly at page 13, lines 3-5. Support for the amendments to claim 18 is found throughout the instant specification and particularly at page 11, lines 5-11 and in Examples 8 and 9. As such, these amendments do not introduce new matter. Applicants respectfully request their entry.

Claims 20-25 have been newly added with this response. Support for newly added claim 20 is found throughout the instant specification and particularly at page 11, lines 5-11. Support for newly added claim 21 is found throughout the instant specification and particularly in Examples 8 and 9. Support for newly added claim 22 is found throughout the instant specification and particularly at page 12, lines 20-21 and in Examples 8 and 9. Support for newly added claim 23 is found throughout the instant specification and particularly in Examples 8 and 9. Support for newly added claim 24 is found throughout the instant specification and particularly at page 9, lines 11-15. Support for newly added claim 25 is found throughout the instant specification and particularly in Examples 8 and 9. As such, these amendments do not introduce new matter. Applicants respectfully request their entry.

**II. In the claims:**

1. (Canceled)

2. (Canceled)

3. (Currently amended) A method ~~according to claim 2~~ of generating an anti-tumor cell immune response in a tumor-bearing mammal comprising the step of administering to said mammal a composition comprising a complex, said complex comprising a cationic molecule and an immunologically active nucleic acid sequence that does not encode for an expressible tumor-associated antigen, wherein said composition is administered in an amount effective to stimulate an immune response against said tumor, and, wherein said immunologically active nucleic acid sequence is a bacterially derived plasmid comprisinges CpG rich motifs.

4. (Currently amended) A method according to claim ~~1~~ 3, wherein said step of administering is accomplished by intra-tumoral administration or administration into a body cavity compartment containing a tumor.

5. (Currently amended) A method according to claim ~~1~~ 3, wherein said step of administering is chosen from aerosolization, intravenous injection, ~~oral~~, intraperitoneal, intranasal, topical, and transmucosal administration.

6. (Currently amended) A method according to claim ~~1~~ 3, wherein said anti-tumor cell response is a systemic response.

7. (Currently amended) A method of generating a protective anti-tumor cell immune response in a tumor-bearing mammal comprising the step of administering to said mammal a composition comprising a complex, wherein said complex comprises a cationic molecule and an immunologically active nucleic acid sequence comprising CpG motifs that does not encode for an expressible tumor-associated antigen, wherein said complex is ~~provided~~ administered in an amount effective to stimulate ~~said anti-tumor cell~~ an immune response against said tumor~~, and wherein said administration is for the purpose of stimulating said protective anti-tumor cell immune response~~.

8. (Canceled)

9. (Original) A method according to claim 7, wherein said immunologically active nucleic acid sequence is bacterially derived.

10. (Original) A method according to claim 7, wherein said immunologically active nucleic acid sequence is a plasmid.

11. (Original) A method according to claim 7, wherein said immunologically active nucleic acid sequence comprises genomic bacterial DNA.

12. (Original) A method according to claim 7, wherein said immunologically active nucleic acid sequence is a fragment.

13. (Canceled)

14. (Original) A method according to claim 7, wherein said step of administering is accomplished by intra-tumoral administration or administration into a body cavity compartment containing a tumor.

15. (Currently amended) A method according to claim 7, wherein said step of administering is chosen from aerosolization, intravenous injection, ~~oral~~, intraperitoneal, intranasal, topical, and transmucosal

administration.

16. (Currently amended) A method according to claim 7, wherein said protective anti-tumor cell immune response is a systemic response.

17. (Canceled)

18. (Currently amended) A composition for generating a protective anti-tumor cell immune response in a tumor-bearing mammal ~~comprising~~ consisting essentially of:
a cationic lipid ~~molecule~~;
and a immunologically active nucleic acid sequence comprising CpG motifs ~~without an expressible cDNA insert~~, wherein said immunologically active nucleic acid sequence is selected from the group consisting of plasmid DNA and genomic DNA; and, optionally, an adjuvant.

19. (Currently amended) A composition according to claim 18 wherein said cationic lipid ~~molecule~~ is GL-67.

20. (New) A method according to claim 7, wherein said nucleic acid sequence is selected from the group comprising genomic DNA, messenger RNA, and ribosomal RNA.

21. (New) A method according to claim 7, wherein said immune response comprises immune memory against the tumor.

22. (New) A method according to claim 7, wherein said immune response comprises an adaptive immune response against the tumor.

23. (New) A method according to claim 7, wherein said immune response eliminates tumor distal to the treatment site.

24. (New) A method according to claim 7, wherein said immune response comprises an immune response selected from one of the following responses: an inflammatory response, a humoral response, a cellular response, a Th1 type response, or a Th2 type response.

25. (New) A method according to claim 24, wherein said immune response eliminates tumor distal to the treatment site.

**III. Claim Rejections:**

**Claim rejections under 35 U.S.C. § 112, first paragraph**

Claims 1-19 stand rejected under 35 U.S.C. § 112, first paragraph because the specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the invention commensurate in scope with the pending claims. Applicants respectfully traverse.

The Office has set forth several issues, addressed individually below.

1) The Office alleges that it is not apparent how a skilled artisan, without any undue experimentation, practices the claimed invention drawn to a cancer treatment by using an immunologically active non-CpG motif containing nucleic acid sequence.

Applicants thank the Examiner for acknowledging that 1) a method of generating an anti-tumor cell immune response in a tumor-bearing mammal comprising administering a complex of GL-67 and an immunologically active CpG motif containing nucleic acid sequence and 2) a method of prolonging the survival of a tumor-bearing animal comprising administering a complex of GL-67 and an immunologically active CpG motif containing nucleic acid sequence are all enabled by the instant specification

In the interest of furthering prosecution, Applicants have amended the instant claims to require the immunologically active nucleic acid sequence to comprise CpG motifs. Applicants have also amended the claims to require a tumor-bearing mammal in the practice of the claimed methods. Therefore, insofar as the above rejection applies to these issues, Applicants assert that these amendments render them moot.

2) The claims have correctly been interpreted as embracing non-lipid cationic molecules. The Office alleges that the instant specification as a whole is not enabling for making and using a complex comprising a cationic molecules and an immunologically active nucleic acid sequence where the cationic molecule is other than a cationic lipid. The Office further alleges that, with respect to claims 7, 18, and those dependent therefrom, the specification is only enabling where the cationic lipid GL-67 is utilized in the methods.

Applicants thank the Examiner for acknowledging that the making and use of a complex comprising a cationic lipid compound and an immunologically active CpG motif containing nucleic acid sequence is enabled by the instant specification.

However, Applicants assert that the instant specification provides sufficient guidance to the skilled artisan to make and use a complex comprising a cationic molecule: immunologically active nucleic acid sequence even where the cationic molecule is not a cationic lipid. Further with respect to claims 7, 18, and those dependent therefrom, the specification is enabling for cationic lipid compounds other than GL-67. The specification is enabling because 1) it specifies the cationic molecules, including cationic lipids, that are suitable in the practice of the instant invention and 2) the specified cationic molecules were in wide use by those of ordinary skill in the art at the time of filing.

The specification identifies to the skilled artisan the cationic molecules suitable in the practice of the instant invention as those "that have been employed in the art to effectuate delivery of biologically active molecules to the cells of mammals..." (see page 14, third full paragraph, first sentence.) Therefore, the skilled artisan is directed to make and use those cationic molecules which have demonstrated delivery of nucleic acids to mammalian cells in the practice of the instant invention. The specification incorporates by reference a large number of such cationic molecules useful in the practice of the instant invention including, for example, the cationic lipids "DOTMA", "DOGS", and DC-CHOL (see page 10, first full paragraph, third and fourth sentences that incorporates the enclosed WO 98/02191.) In addition, cationic molecules that effectuated delivery of nucleic acids to mammalian cells were widely known and widely used by those of ordinary skill in the art at the time the instant application was filed. Review articles that were published before or around the time of the instant filing demonstrate this depth of available knowledge. These articles describe nucleic acid delivery systems using various cationic molecules such as polyamines, polyethyleninimes, and cationic lipids. (See enclosed Garnett, M.C., *Crit. Rev. Ther. Drug Carrier Syst.*, 1999, 16(2): 147; Remy et al., *Adv. Drug Deliv. Rev.*, 1998, 30: 85.) Applicants note that the specification need not disclose and preferably omits that which is well-known to the skilled artisan and already available to the public [MPEP 2164.05(a)].

In combination with the extensive knowledge of nucleic acid delivery systems in the art at the time of filing, the instant specification provides working examples of the instant invention using the cationic lipid GL-67. The examples provide extensive guidance for the practice of the instant invention such as delivery methods, animal models, and end-point assays to measure anti-tumor immune responses and survival. Therefore, Applicants assert that the skilled artisan had the ability to make and use the instant invention at the time of filing based on the direction provided by the instant specification and the level of skill in the art.

Moreover, Applicants point to several articles, published subsequent to the instant application, that demonstrate the ability of cationic lipid: DNA complexes to induce anti-tumor cell immune responses following administration to tumor-bearing mammals. These articles utilize various cationic lipids, such as GL-67, DC-CHOL, and DOTMA, in their methods.

In Dow et al., anti-tumor effects were observed via the reduction of tumor burden and prolonged

survival times in mice treated with cationic lipid: DNA complexes (both DOTMA and DOTAP cationic lipids were effective; see enclosed Dow et al., *J. Immunol.*, 1999, 163(3): 1552 at page 1553, first column, second full paragraph in entirety and page 1556, Figure 4.) Anti-tumor effects were also observed by Lanuti et al. in the long-term survival (>90 days) of tumor-bearing mice that were treated with cationic lipid: DNA complexes (both GL-67 and DC-CHOL cationic lipids were effective; see Lanuti et al., *Cancer Res.*, 2000, 60(11): 2955 at page 2957, Figure 1, panel B.) Applicants are not using subsequent work to supplement the disclosure of the application. Rather, the subsequent work, which utilize methods similar to those described in the instant specification, is cited to demonstrate that the utility asserted and taught is supported by later research.

As such, Applicants respectfully assert that the specification enables the skilled artisan make and use a complex comprising a cationic molecule: immunologically active nucleic acid sequence. Further with respect to claims 7, 18, and those dependent therefrom, the specification is enabling for cationic lipid compounds other than GL-67. It specifies the cationic molecules that are suitable in the practice of the instant invention; the specified cationic molecules were in wide use by those of ordinary skill in the art at the time of filing; several working examples of the instant invention are provided; and subsequent research demonstrates that the disclosed methods are effective. In light of the above arguments, Applicants respectfully request withdrawal of this rejection.

**Claim rejections under 35 U.S.C. § 102(e)**

Claims 1-18 stand rejected under 35 U.S.C. § 102(e) as being allegedly anticipated by U.S. Patent No. 6,207,646 (the '646 patent), U.S. Patent No. 6,218,371 (the '371 patent), or U.S. Patent No. 6,429,199 (the '199 patent).

The Office alleges that the above patents anticipate the instant invention because they teach that a cationic lipid can be utilized in combination with a CpG motif containing nucleic acid polymer as an immunostimulatory complex to induce an immune response to a target cancer antigen. Applicants respectfully traverse. With respect to the claimed methods of claims 3, 7, and those dependent therefrom, the '646, '371, and '199 patents do not and cannot anticipate the instant invention because the above patents do not teach or suggest a method to generate an anti-tumor immune response in a tumor-bearing animal in the absence of a tumor-associated antigen.

Applicants have been unable to identify an enabling teaching or suggestion in the passages cited by the Office disclosing a method utilizing the instant compositions to generate an anti-tumor immune response or to prolong the survival of a tumor-bearing animal in the absence of a tumor-associated antigen. For example, one of the sections cited in the "646 patent teaches:

> ...the immunostimulatory nucleic acid molecules can be used to treat or prevent or ameliorate an immune system deficiency (e.g. a tumor or cancer... (column 6, lines 55-56.)

Applicants assert that the cited text does not represent an enabling disclosure that anticipates the methods as claimed. Further, a cited portion of the '371 patent teaches:

> The methods of the invention are useful for treating cancer by stimulating an antigen specific immune response against a cancer antigen. A 'cancer antigen' as used herein is a compound, such as a peptide, associated with a tumor or cancer cell surface and which is capable of provoking an immune response when expressed on the surface of an antigen presenting cell in the context of an MHC molecule. (column 7, lines 1-7)

This also does not represent an enabling disclosure that anticipates the methods as claimed.

Within the art cited by the Office, the '371 patent contains a single teaching where a tumor-bearing model is treated and where anti-tumor effects are evaluated. Mice bearing 38C13 murine B cell lymphoma tumors were treated with compositions containing CpG oligonucleotides with or without an ID/GM-CSF fusion protein (see '371, column 36, example 5 and Figure 5.) (Applicants note that these compositions did not comprise cationic molecules.) The Id/GM-CSF protein is a fusion between the highly specific tumor-associated antigen for the 38C13 murine B cell lymphoma and the cytokine GM-CSF. Mice treated with the composition containing the CpG oligonucleotide without the antigen developed tumor and died with kinetics similar to the untreated group. Only mice treated with the composition containing the CpG oligonucleotide and Id/GM-CSF antigen demonstrated anti-tumor effects, which were of an undisclosed nature, in the form of extended survival. Therefore, the '371 patent does not disclose a method to treat a tumor-bearing mammal where an anti-tumor immune response is generated in the absence of antigen.

With respect to the claimed composition in claim 18, the '646, '371, and '199 patents do not and cannot anticipate claim 18 because the compositions disclosed within the above patents do not teach or suggest a composition effective to generate a protective anti-tumor cell immune response in a tumor-bearing animal in the absence of a tumor-associated antigen. Applicants have been unable to identify a teaching or suggestion in the passages cited by the Office disclosing such a composition.

Further with respect to newly added claims 21, 23, and 25, the '646, '371, and '199 patents do not and cannot anticipate these claims because the methods disclosed within the above patents do not teach or suggest the generation of an anti-tumor immune response in a tumor-bearing animal in the absence of a tumor-associated antigen wherein the immune response comprises immune memory against the tumor or eliminates tumor distal to the treatment site.

In light of the above arguments, Applicants respectfully request withdrawal of this rejection.

**Claim rejections under 35 U.S.C. § 103(a)**

Claims 1-18 stand rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Erbacher et al. (US 2001/0048939) taken with U.S. Patent No. 6,207,646 (the '646 patent), U.S. Patent No. 6,218,371 (the '371 patent), or U.S. Patent No. 6,429,199 (the '199 patent).

The Office alleges that it would have been obvious for one of ordinary skill to employ a cationic lipid complex composed of cytofectin lipid:CpG containing plasmid fragments for use in therapeutic vaccines in a tumor-bearing animal. Applicants respectfully traverse.

As discussed above, the '371 patent does not disclose a method to treat a tumor-bearing mammal where an anti-tumor immune response is generated in the absence of antigen. The Office admits that Erbacher does not cure this defect (see Office Action mailed January 14, 2004, page 18, first complete sentence.) Therefore, the Office has failed to establish a prima facie case of obviousness. In light of this, Applicants respectfully request withdrawal of this rejection.

**IV. Conclusion**

No fee is deemed necessary in connection with the filing of this communication. However, if any fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 07-1074.

Respectfully submitted,

7/14/04
Date

Jennifer D. Tousignant
Registration No. 54,498
Telephone: (508) 270-2499
Facsimile: (508) 872-5415

GENZYME CORPORATION
15 Pleasant Street Connector
P.O. Box 9322
Framingham, Massachusetts 01701-9322